## REMARKS

Reconsideration is requested.

Claims 2, 6-7, 15-18 and 26-30 are pending. Claims 1, 2-5, 8-14 and 19-25 have been canceled, without prejudice. Claims 26-30 have been added. Claims 26 and 27, and claims 28-30 dependent there from, are similar to claim 2 in the recitation of the composition components and are specific for the recited FP, FL and SL peptides, as further detailed below. No new matter has been added.

The Section 112, first paragraph "enablement", rejection of claims 2, 3, 6, 7 and 15-18 is traversed.

The Examiner asserts that

> **the claims may encompass chemical modification at single or multiple amino acid locations throughout any given peptide.** See, page 2 of the Office Action dated November 17, 2004 (emphasis in original).

The applicants respectfully submit that the claims do not recite chemical modifications at single or multiple amino acid locations throughout any given peptide. The claimed immunoretroid peptides include modifications on the N- and/or C- terminus of with the following groups

Q (H-, $H_2N$-, P-HN-, RR'N-, $H_2NCO$-, RR'NCO-, RCO-),

M (H-, -COOH, -COOR, -$CONH_2$, -CONRR' and -NHCOR),

X (H-, P-, R- and RCO-), and

Y (-OH, -OR, -$NH_2$, and -NRR');

where

R and R' are independently selected from the group consisting of hydrogen, $C_{1-25}$ alkyl, $C_{3-25}$ allyl, $C_{6-25}$ aryl, benzyl, 2-phenyl-ethyl, methyl-fluorenyl, glycolamide and benzhydrylglycolamide; and

P is a protecting group.

The claimed immunoretroid peptides include modifications in the peptide backbone, as compared with the recited native peptides, in substituting -NH-CO- groups for -CO-NH groups. The claims do not recite chemical modifications at single or multiple amino acid locations throughout any given peptide. The modification of peptides with protecting groups or other groups as presently claimed are well known and commonly practiced by those of ordinary skill in the art.

The Examiner asserts that

> "the skilled artisan cannot reasonable predict the effects of such changes [i.e., "the chemical modifications at single or multiple amino acid locations throughout any given peptide"] on the immunological and biochemical properties of any given peptide." Id.

As noted above, the claims do not recite chemical modifications at single or multiple amino acid locations throughout any given peptide.

As for the immunoretroid modifications of the recited basic peptide, the applicants submit that one of ordinary skill in the art is taught by the present application and the generally advanced knowledge in the art how to make the claimed invention. Moreover, the claimed vaccine and compositions require that the immunoretroids bind to an antibody or antibody fragment to the peptide with at least equal affinity as the peptide. Methods are well known for testing for binding affinity of antibodies and antibody fragments. Finally, the claims define a reasonable number of possible

variations such that even if one of ordinary skill in the art were required to make and test each of the claimed immunoretroids, such testing would not require an undue amount of experimentation.

Specifically, for example, the Examiner will appreciate that the claims relate to immunoretroids of the following three peptides: FP peptide, FL peptide and SL peptide, wherein the peptide sequences are provided in the Sequence Listing, with an additional Cys at the N-terminal end to facilitate attachment. These peptides have the following amino acids, in the order of appearance from the N- to C- terminus - wherein the "R" group of each amino acid is also provided with a subscript designating the amino acid number or, in the terms of formula (II) of the application and claims, the value of the subscript "k":

**Cys; $R_1 = CH_2SH$**
**Gly; $R_2 = H$**
**Ser; $R_3 = CH_2OH$**
**Gly; $R_4 = H$**
**Val; $R_5 = CH(CH_3)_2$**
**Arg; $R_6 = (CH_2)_3NHC(NH)NH_2$**
**Gly; $R_7 = H$**
**Asp; $R_8 = CH_2COOH$**
**Phe/Phe/Ser; $R_9 = CH_2(C_6H_5)/ CH_2(C_6H_5)/CH_2OH$**
**Gly; $R_{10} = H$**
**Ser; $R_{11} = CH_2OH$**
**Leu; $R_{12} = CH_2CH(CH_3)_2$**
**Ala; $R_{13} = CH_3$**
**Pro/Leu/Leu; $R_{14} = C_3H_6/ CH_2CH(CH_3)_2/ CH_2CH(CH_3)_2$**
**Arg; $R_{15} = (CH_2)_3NHC(NH)NH_2$**
**Val; $R_{16} = CH(CH_3)_2$**
**Ala; $R_{17} = CH_3$**
**Arg; $R_{18} = (CH_2)_3NHC(NH)NH_2$**
**Gln; $R_{19} = CH_2CH_2C(O)NH_2$**
**Leu; $R_{20} = CH_2CH(CH_3)_2$**

The amino acids at positions 9 and 14 have the indicated variability as between the recited FP peptide, FL peptide and SL peptide.

The values of i, j, k and n for the 20 amino acid sequences of the FP peptide, FL peptide and SL peptide of the Sequence Listing, define the following 190 "peptides", which have been arbitrarily numbered for illustration purposes wherein the values for A, B, Q, M, T and L are provided above:

| Peptide No. | k (aa #s) | i | j | n | A | B |
|---|---|---|---|---|---|---|
| 1 | 2-19 | 1 | 19 | 20 | Q | M |
| 2 | 3-19 | 2 | 19 | 20 | T | M |
| 3 | 4-19 | 3 | 19 | 20 | T | M |
| 4 | 5-19 | 4 | 19 | 20 | T | M |
| 5 | 6-19 | 5 | 19 | 20 | T | M |
| 6 | 7-19 | 6 | 19 | 20 | T | M |
| 7 | 8-19 | 7 | 19 | 20 | T | M |
| 8 | 9-19 | 8 | 19 | 20 | T | M |
| 9 | 10-19 | 9 | 19 | 20 | T | M |
| 10 | 11-19 | 10 | 19 | 20 | T | M |
| 11 | 12-19 | 11 | 19 | 20 | T | M |
| 12 | 13-19 | 12 | 19 | 20 | T | M |
| 13 | 14-19 | 13 | 19 | 20 | T | M |
| 14 | 15-19 | 14 | 19 | 20 | T | M |
| 15 | 16-19 | 15 | 19 | 20 | T | M |
| 16 | 17-19 | 16 | 19 | 20 | T | M |
| 17 | 18-19 | 17 | 19 | 20 | T | M |
| 18 | 19 | 18 | 19 | 20 | T | M |
| 19 | 0 | 19 | 19 | 20 | T | M |
| 20 | 2-18 | 1 | 18 | 20 | Q | L |
| 21 | 3-18 | 2 | 18 | 20 | T | L |
| 22 | 4-18 | 3 | 18 | 20 | T | L |
| 23 | 5-18 | 4 | 18 | 20 | T | L |
| 24 | 6-18 | 5 | 18 | 20 | T | L |
| 25 | 7-18 | 6 | 18 | 20 | T | L |
| 26 | 8-18 | 7 | 18 | 20 | T | L |
| 27 | 9-18 | 8 | 18 | 20 | T | L |
| 28 | 10-18 | 9 | 18 | 20 | T | L |
| 29 | 11-18 | 10 | 18 | 20 | T | L |
| 30 | 12-18 | 11 | 18 | 20 | T | L |
| 31 | 13-18 | 12 | 18 | 20 | T | L |
| 32 | 14-18 | 13 | 18 | 20 | T | L |

| Peptide No. | k (aa #s) | i | j | n | A | B |
|---|---|---|---|---|---|---|
| 33 | 15-18 | 14 | 18 | 20 | T | L |
| 34 | 16-18 | 15 | 18 | 20 | T | L |
| 35 | 17-18 | 16 | 18 | 20 | T | L |
| 36 | 18 | 17 | 18 | 20 | T | L |
| 37 | 0 | 18 | 18 | 20 | T | L |
| 38 | 2-17 | 1 | 17 | 20 | Q | L |
| 39 | 3-17 | 2 | 17 | 20 | T | L |
| 40 | 4-17 | 3 | 17 | 20 | T | L |
| 41 | 5-17 | 4 | 17 | 20 | T | L |
| 42 | 6-17 | 5 | 17 | 20 | T | L |
| 43 | 7-17 | 6 | 17 | 20 | T | L |
| 44 | 8-17 | 7 | 17 | 20 | T | L |
| 45 | 9-17 | 8 | 17 | 20 | T | L |
| 46 | 10-17 | 9 | 17 | 20 | T | L |
| 47 | 11-17 | 10 | 17 | 20 | T | L |
| 48 | 12-17 | 11 | 17 | 20 | T | L |
| 49 | 13-17 | 12 | 17 | 20 | T | L |
| 50 | 14-17 | 13 | 17 | 20 | T | L |
| 51 | 15-17 | 14 | 17 | 20 | T | L |
| 52 | 16-17 | 15 | 17 | 20 | T | L |
| 53 | 17 | 16 | 17 | 20 | T | L |
| 54 | 0 | 17 | 17 | 20 | T | L |
| 55 | 2-16 | 1 | 16 | 20 | Q | L |
| 56 | 3-16 | 2 | 16 | 20 | T | L |
| 57 | 4-16 | 3 | 16 | 20 | T | L |
| 58 | 5-16 | 4 | 16 | 20 | T | L |
| 59 | 6-16 | 5 | 16 | 20 | T | L |
| 60 | 7-16 | 6 | 16 | 20 | T | L |
| 61 | 8-16 | 7 | 16 | 20 | T | L |
| 62 | 9-16 | 8 | 16 | 20 | T | L |
| 63 | 10-16 | 9 | 16 | 20 | T | L |
| 64 | 11-16 | 10 | 16 | 20 | T | L |
| 65 | 12-16 | 11 | 16 | 20 | T | L |
| 66 | 13-16 | 12 | 16 | 20 | T | L |
| 67 | 14-16 | 13 | 16 | 20 | T | L |
| 68 | 15-16 | 14 | 16 | 20 | T | L |
| 69 | 16 | 15 | 16 | 20 | T | L |
| 70 | 0 | 16 | 16 | 20 | T | L |
| 71 | 2-15 | 1 | 15 | 20 | Q | L |
| 72 | 3-15 | 2 | 15 | 20 | T | L |
| 73 | 4-15 | 3 | 15 | 20 | T | L |
| 74 | 5-15 | 4 | 15 | 20 | T | L |
| 75 | 6-15 | 5 | 15 | 20 | T | L |
| 76 | 7-15 | 6 | 15 | 20 | T | L |
| 77 | 8-15 | 7 | 15 | 20 | T | L |

| Peptide No. | k (aa #s) | i | j | n | A | B |
|---|---|---|---|---|---|---|
| 78 | 9-15 | 8 | 15 | 20 | T | L |
| 79 | 10-15 | 9 | 15 | 20 | T | L |
| 80 | 11-15 | 10 | 15 | 20 | T | L |
| 81 | 12-15 | 11 | 15 | 20 | T | L |
| 82 | 13-15 | 12 | 15 | 20 | T | L |
| 83 | 14-15 | 13 | 15 | 20 | T | L |
| 84 | 15 | 14 | 15 | 20 | T | L |
| 85 | 0 | 15 | 15 | 20 | T | L |
| 86 | 2-14 | 1 | 14 | 20 | Q | L |
| 87 | 3-14 | 2 | 14 | 20 | T | L |
| 88 | 4-14 | 3 | 14 | 20 | T | L |
| 89 | 5-14 | 4 | 14 | 20 | T | L |
| 90 | 6-14 | 5 | 14 | 20 | T | L |
| 91 | 7-14 | 6 | 14 | 20 | T | L |
| 92 | 8-14 | 7 | 14 | 20 | T | L |
| 93 | 9-14 | 8 | 14 | 20 | T | L |
| 94 | 10-14 | 9 | 14 | 20 | T | L |
| 95 | 11-14 | 10 | 14 | 20 | T | L |
| 96 | 12-14 | 11 | 14 | 20 | T | L |
| 97 | 13-14 | 12 | 14 | 20 | T | L |
| 98 | 14 | 13 | 14 | 20 | T | L |
| 99 | 0 | 14 | 14 | 20 | T | L |
| 100 | 2-13 | 1 | 13 | 20 | Q | L |
| 101 | 3-13 | 2 | 13 | 20 | T | L |
| 102 | 4-13 | 3 | 13 | 20 | T | L |
| 103 | 5-13 | 4 | 13 | 20 | T | L |
| 104 | 6-13 | 5 | 13 | 20 | T | L |
| 105 | 7-13 | 6 | 13 | 20 | T | L |
| 106 | 8-13 | 7 | 13 | 20 | T | L |
| 107 | 9-13 | 8 | 13 | 20 | T | L |
| 108 | 10-13 | 9 | 13 | 20 | T | L |
| 109 | 11-13 | 10 | 13 | 20 | T | L |
| 110 | 12-13 | 11 | 13 | 20 | T | L |
| 111 | 13 | 12 | 13 | 20 | T | L |
| 112 | 0 | 13 | 13 | 20 | T | L |
| 113 | 2-12 | 1 | 12 | 20 | Q | L |
| 114 | 3-12 | 2 | 12 | 20 | T | L |
| 115 | 4-12 | 3 | 12 | 20 | T | L |
| 116 | 5-12 | 4 | 12 | 20 | T | L |
| 117 | 6-12 | 5 | 12 | 20 | T | L |
| 118 | 7-12 | 6 | 12 | 20 | T | L |
| 119 | 8-12 | 7 | 12 | 20 | T | L |
| 120 | 9-12 | 8 | 12 | 20 | T | L |
| 121 | 10-12 | 9 | 12 | 20 | T | L |
| 122 | 11-12 | 10 | 12 | 20 | T | L |

| Peptide No. | k (aa #s) | i | j | n | A | B |
|---|---|---|---|---|---|---|
| 123 | 12 | 11 | 12 | 20 | T | L |
| 124 | 0 | 12 | 12 | 20 | T | L |
| 125 | 2-11 | 1 | 11 | 20 | Q | L |
| 126 | 3-11 | 2 | 11 | 20 | T | L |
| 127 | 4-11 | 3 | 11 | 20 | T | L |
| 128 | 5-11 | 4 | 11 | 20 | T | L |
| 129 | 6-11 | 5 | 11 | 20 | T | L |
| 130 | 7-11 | 6 | 11 | 20 | T | L |
| 131 | 8-11 | 7 | 11 | 20 | T | L |
| 132 | 9-11 | 8 | 11 | 20 | T | L |
| 133 | 10-11 | 9 | 11 | 20 | T | L |
| 134 | 11 | 10 | 11 | 20 | T | L |
| 135 | 0 | 11 | 11 | 20 | T | L |
| 136 | 2-10 | 1 | 10 | 20 | Q | L |
| 137 | 3-10 | 2 | 10 | 20 | T | L |
| 138 | 4-10 | 3 | 10 | 20 | T | L |
| 139 | 5-10 | 4 | 10 | 20 | T | L |
| 140 | 6-10 | 5 | 10 | 20 | T | L |
| 141 | 7-10 | 6 | 10 | 20 | T | L |
| 142 | 8-10 | 7 | 10 | 20 | T | L |
| 143 | 9-10 | 8 | 10 | 20 | T | L |
| 144 | 10 | 9 | 10 | 20 | T | L |
| 145 | 0 | 10 | 10 | 20 | T | L |
| 146 | 2-9 | 1 | 9 | 20 | Q | L |
| 147 | 3-9 | 2 | 9 | 20 | T | L |
| 148 | 4-9 | 3 | 9 | 20 | T | L |
| 149 | 5-9 | 4 | 9 | 20 | T | L |
| 150 | 6-9 | 5 | 9 | 20 | T | L |
| 151 | 7-9 | 6 | 9 | 20 | T | L |
| 152 | 8-9 | 7 | 9 | 20 | T | L |
| 153 | 9 | 8 | 9 | 20 | T | L |
| 154 | 0 | 9 | 9 | 20 | T | L |
| 155 | 2-8 | 1 | 8 | 20 | Q | L |
| 156 | 3-8 | 2 | 8 | 20 | T | L |
| 157 | 4-8 | 3 | 8 | 20 | T | L |
| 158 | 5-8 | 4 | 8 | 20 | T | L |
| 159 | 6-8 | 5 | 8 | 20 | T | L |
| 160 | 7-8 | 6 | 8 | 20 | T | L |
| 161 | 8 | 7 | 8 | 20 | T | L |
| 162 | 0 | 8 | 8 | 20 | T | L |
| 163 | 2-7 | 1 | 7 | 20 | Q | L |
| 164 | 3-7 | 2 | 7 | 20 | T | L |
| 165 | 4-7 | 3 | 7 | 20 | T | L |
| 166 | 5-7 | 4 | 7 | 20 | T | L |
| 167 | 6-7 | 5 | 7 | 20 | T | L |

| Peptide No. | k (aa #s) | i | j | n | A | B |
|---|---|---|---|---|---|---|
| 168 | 7 | 6 | 7 | 20 | T | L |
| 169 | 0 | 7 | 7 | 20 | T | L |
| 170 | 2-6 | 1 | 6 | 20 | Q | L |
| 171 | 3-6 | 2 | 6 | 20 | T | L |
| 172 | 4-6 | 3 | 6 | 20 | T | L |
| 173 | 5-6 | 4 | 6 | 20 | T | L |
| 174 | 6 | 5 | 6 | 20 | T | L |
| 175 | 0 | 6 | 6 | 20 | T | L |
| 176 | 2-5 | 1 | 5 | 20 | Q | L |
| 177 | 3-5 | 2 | 5 | 20 | T | L |
| 178 | 4-5 | 3 | 5 | 20 | T | L |
| 179 | 5 | 4 | 5 | 20 | T | L |
| 180 | 0 | 5 | 5 | 20 | T | L |
| 181 | 2-4 | 1 | 4 | 20 | Q | L |
| 182 | 3-4 | 2 | 4 | 20 | T | L |
| 183 | 4 | 3 | 4 | 20 | T | L |
| 184 | 0 | 4 | 4 | 20 | T | L |
| 185 | 2-3 | 1 | 3 | 20 | Q | L |
| 186 | 3 | 2 | 3 | 20 | T | L |
| 187 | 0 | 3 | 3 | 20 | T | L |
| 188 | 2 | 1 | 2 | 20 | Q | L |
| 189 | 0 | 2 | 2 | 20 | T | L |
| 190 | 0 | 1 | 1 | 20 | Q | L |

One of ordinary skill in the art will appreciate that the following examples of the immunoretroids of formula (II) may be constructed, without undue experimentation, and screened for the required activity:

**Example of peptides of claims:**

**Peptide 1 (from above table and formula II)**
Q-CH($R_1$)-NH-CO-CH($R_2$)-NH- CO-CH($R_3$)-NH- CO-CH($R_4$)-NH- CO-CH($R_5$)-NH- CO-CH($R_6$)-NH- CO-CH($R_7$)-NH- CO-CH($R_8$)-NH- CO-CH($R_9$)-NH- CO-CH($R_{10}$)-NH- CO-CH($R_{11}$)-NH- CO-CH($R_{12}$)-NH- CO-CH($R_{13}$)-NH- CO-CH($R_{14}$)-NH- CO-CH($R_{15}$)-NH- CO-CH($R_{16}$)-NH- CO-CH($R_{17}$)-NH- CO-CH($R_{18}$)-NH- CO-CH($R_{19}$)-NH-CO-CH($R_{20}$)-M

**Peptide 2 (from above table and formula II)**
T-CH($R_2$)-NH- CO-CH($R_3$)-NH- CO-CH($R_4$)-NH- CO-CH($R_5$)-NH- CO-CH($R_6$)-NH- CO-CH($R_7$)-NH- CO-CH($R_8$)-NH- CO-CH($R_9$)-NH- CO-CH($R_{10}$)-NH- CO-CH($R_{11}$)-NH- CO-

$CH(R_{12})$-NH- CO-$CH(R_{13})$-NH- CO-$CH(R_{14})$-NH- CO-$CH(R_{15})$-NH- CO-$CH(R_{16})$-NH- CO-$CH(R_{17})$-NH- CO-$CH(R_{18})$-NH- CO-$CH(R_{19})$-NH-CO-$CH(R_{20})$-M

Where T= X-HN-$CH(R_1)$-CO-

**Peptide 3 (from above table and formula II)**
T-$CH(R_3)$-NH- CO-$CH(R_4)$-NH- CO-$CH(R_5)$-NH- CO-$CH(R_6)$-NH- CO-$CH(R_7)$-NH- CO-$CH(R_8)$-NH- CO-$CH(R_9)$-NH- CO-$CH(R_{10})$-NH- CO-$CH(R_{11})$-NH- CO-$CH(R_{12})$-NH- CO-$CH(R_{13})$-NH- CO-$CH(R_{14})$-NH- CO-$CH(R_{15})$-NH- CO-$CH(R_{16})$-NH- CO-$CH(R_{17})$-NH- CO-$CH(R_{18})$-NH- CO-$CH(R_{19})$-NH-CO-$CH(R_{20})$-M

Where T= X-HN-$CH(R_1)$-CO-NH-$CH(R_2)$CO-NH-

**Peptide 4 (from above table and formula II)**
T-$CH(R_4)$-NH- CO-$CH(R_5)$-NH- CO-$CH(R_6)$-NH- CO-$CH(R_7)$-NH- CO-$CH(R_8)$-NH- CO-$CH(R_9)$-NH- CO-$CH(R_{10})$-NH- CO-$CH(R_{11})$-NH- CO-$CH(R_{12})$-NH- CO-$CH(R_{13})$-NH- CO-$CH(R_{14})$-NH- CO-$CH(R_{15})$-NH- CO-$CH(R_{16})$-NH- CO-$CH(R_{17})$-NH- CO-$CH(R_{18})$-NH- CO-$CH(R_{19})$-NH-CO-$CH(R_{20})$-M

Where T= X-HN-$CH(R_1)$-CO-NH-$CH(R_2)$CO-NH- $CH(R_3)$CO-NH-

**Peptide 5 (from above table and formula II)**
T-$CH(R_5)$-NH- CO-$CH(R_6)$-NH- CO-$CH(R_7)$-NH- CO-$CH(R_8)$-NH- CO-$CH(R_9)$-NH- CO-$CH(R_{10})$-NH- CO-$CH(R_{11})$-NH- CO-$CH(R_{12})$-NH- CO-$CH(R_{13})$-NH- CO-$CH(R_{14})$-NH- CO-$CH(R_{15})$-NH- CO-$CH(R_{16})$-NH- CO-$CH(R_{17})$-NH- CO-$CH(R_{18})$-NH- CO-$CH(R_{19})$-NH-CO-$CH(R_{20})$-M

Where T= X-HN-$CH(R_1)$-CO-NH-$CH(R_2)$CO-NH- $CH(R_3)$CO- NH-$CH(R_4)$CO-NH-

.....

**Peptide 19 (from above table and formula II)**
T-$CH(R_{19})$-NH- CO-$CH(R_{20})$-M

Where T= X-HN-$CH(R_1)$-CO-NH-$CH(R_2)$CO-NH- $CH(R_3)$CO- NH-$CH(R_4)$CO-NH-$CH(R_5)$CO-NH- $CH(R_6)$CO-NH- $CH(R_7)$CO-NH- $CH(R_8)$CO-NH- $CH(R_9)$CO-NH-$CH(R_{10})$CO-NH- $CH(R_{11})$CO-NH- $CH(R_{12})$CO-NH- $CH(R_{13})$CO-NH- $CH(R_{14})$CO-NH-$CH(R_{15})$CO-NH- $CH(R_{16})$CO-NH- $CH(R_{17})$CO-NH- $CH(R_{18})$CO-NH-

**Peptide 20 (from above table and formula II)**

Q-$CH(R_1)$-NH-CO-$CH(R_2)$-NH- CO-$CH(R_3)$-NH- CO-$CH(R_4)$-NH- CO-$CH(R_5)$-NH- CO-$CH(R_6)$-NH- CO-$CH(R_7)$-NH- CO-$CH(R_8)$-NH- CO-$CH(R_9)$-NH- CO-$CH(R_{10})$-NH- CO-

$CH(R_{11})$-NH- CO-$CH(R_{12})$-NH- CO-$CH(R_{13})$-NH- CO-$CH(R_{14})$-NH- CO-$CH(R_{15})$-NH- CO-$CH(R_{16})$-NH- CO-$CH(R_{17})$-NH- CO-$CH(R_{18})$-NH- CO-$CH(R_{19})$-CO-NH-$CH(R_{20})$-CO-Y

**Peptide 21 (from above table and formula II)**

T-$CH(R_2)$-NH- CO-$CH(R_3)$-NH- CO-$CH(R_4)$-NH- CO-$CH(R_5)$-NH- CO-$CH(R_6)$-NH- CO-$CH(R_7)$-NH- CO-$CH(R_8)$-NH- CO-$CH(R_9)$-NH- CO-$CH(R_{10})$-NH- CO-$CH(R_{11})$-NH- CO-$CH(R_{12})$-NH- CO-$CH(R_{13})$-NH- CO-$CH(R_{14})$-NH- CO-$CH(R_{15})$-NH- CO-$CH(R_{16})$-NH- CO-$CH(R_{17})$-NH- CO-$CH(R_{18})$-NH- CO-$CH(R_{19})$ -CO-NH-$CH(R_{20})$-CO-Y

Where T= X-HN-$CH(R_1)$-CO-NH-

**Peptide 22 (from above table and formula II)**
T-$CH(R_3)$-NH- CO-$CH(R_4)$-NH- CO-$CH(R_5)$-NH- CO-$CH(R_6)$-NH- CO-$CH(R_7)$-NH- CO-$CH(R_8)$-NH- CO-$CH(R_9)$-NH- CO-$CH(R_{10})$-NH- CO-$CH(R_{11})$-NH- CO-$CH(R_{12})$-NH- CO-$CH(R_{13})$-NH- CO-$CH(R_{14})$-NH- CO-$CH(R_{15})$-NH- CO-$CH(R_{16})$-NH- CO-$CH(R_{17})$-NH- CO-$CH(R_{18})$-NH- CO-$CH(R_{19})$ -CO-NH-$CH(R_{20})$-CO-Y

Where T= X-HN-$CH(R_1)$-CO-NH-$CH(R_2)$CO-NH-
....

Q being selected from the group consisting of H-, $H_2N$-, P-HN-, RR'N-, $H_2NCO$-,

RR'NCO-, RCO-;

M being selected from the group consisting of H-, -COOH, -COOR, $-CONH_2$, -CONRR'

and -NHCOR;

X is selected from the group consisting of H-, P-, R- and RCO-;

R and R' are independently selected from the group consisting of hydrogen, $C_{1\text{-}25}$ alkyl, $C_{3\text{-}25}$ allyl, $C_{6\text{-}25}$ aryl, benzyl, 2-phenyl-ethyl, methyl-fluorenyl, glycolamide and benzhydrylglycolamide; and

P is a protecting group

The specification is submitted to provide more than adequate guidance for one of ordinary skill in the art to make and use the presently claimed invention.

Specifically, for example, the specification provides, as Example 3, an illustration of vaccination of a totally retro-partly inverso peptides corresponding to the major antigenic determinant situated on the protein $VP_1$ of the virus of aphthous fever (foot-and-mouth disease virus, FMDV).

Protein $VP_1$ is known to trigger synthesis of neutralizing antibodies (Ab).

Vaccines exist conventionally in two forms, attenuated or inactivated, but their preparation and their handling present many disadvantages. At the time the present invention, several groups of researchers in the field of FMDV had studied the possibility of producing significant quantities of the protein $VP_1$ by means of genetic engineering techniques. However, the doses needed to induce protection in cattle, as for the natural protein $VP_1$ isolated from viral particles, was still thought to be too high.

Another proposed approach has constituted imitation of the fragment 141-160 of the protein $VP_1$ by chemical synthesis. This fragment in fact corresponds to a particular region of the protein $VP_1$, to which the neutralizing antibody(bodies) attach(es) specifically. On the other hand, this same peptide coupled to a carrier protein induces an immune response in the guinea-pig such that the immunized animal is protected against aphthous fever (these animals are a very good biological model for study of the disease). It has been found that a single injection of conjugated peptide was sufficient to protect infected animals.

However, fundamental research was still thought to be necessary to provide these synthetic peptides with their entire effectiveness as vaccines. In fact, it was often proved to be difficult or even impossible to obtain sufficient neutralizing titres of anti-peptide Ab. This was thought to be related to the problems relating to stabilization of an

"optimum" conformation of a linear sequence, as well as to the rapid degradation of peptides injected into the animal. In the context of the present invention, a study of the antigenic and immunogenic properties of retro-inverso (RI) analogues derived from the immunodominant loop of three variants of serotype A12 of FMDV was undertaken. The sequences of these peptides and of the corresponding RI analogues are shown in Table 8 of the specification. As noted above, a cysteine residue was added in the N-terminal position at the end of coupling.

TABLE 8
Sequences of synthetic peptides (region 141-159) derived from the immunodominant loop of three variants of serotype A12 of the virus of aphthous fever (FMDV).

FP peptide (strain USA) (SEQ ID NO:7) C-G$^{141}$-S-G-V-R-G-D-F-G-S-L-A-P-R-V-A-R-Q-L$^{159}$

FL peptide (SEQ ID NO:8) C-G$^{141}$-S-G-V-R-G-D-F-G-S-L-A-L-R-V-A-R-Q-L$^{159}$

SL peptide (strain A) (SEQ ID NO:9) C-G$^{141}$-S-G-V-R-G-D-S-G-S-L-A-L-R-V-A-R-Q-L$^{159}$

Sequences of the corresponding retro-inverso analogues
HO-m(R or S)Leu-q-r-a-v-r-(*)-a-l-s-G-(**)-d-G-r-v-G-s-G-c-$NH_2$

| | | | | |
|---|---|---|---|---|
| (**) | : | f | f | s |
| (*) | : | p | l | l |

The study of the specification was divided into the following three parts:

1) Study of the antigenic properties of the analogues.

Sera of guinea-pigs immunized against the virus ("antivirion"), protein $VP_1$ ("anti-protein $VP_1$"), against peptide 141-159 (variant USA; "anti-FP peptide") and serum originating from guinea-pigs infected with the virus ("convalescent") are available. Normal serum (negative batch) of the guinea-pig serves as a control. The results are shown on Table 9 of the application. The two RIa and RIb diastereomers were separated, purified by HPLC and tested separately in ELISA. The RI isomer eluted

fastest by HPLC is called RIa, and the 2nd peak eluted (isomer eluted slowest) comprises the isomer called RIb. Only the results with the FP system are shown.

It will be noted that the RI analogues are recognized as well as and often better than the parent FP-L peptide. The results are analogous in the case of the FL and SL peptides.

Inhibition studies were carried out in the BIAcore system. Table 10 of the application shows the amounts of analogues which are necessary to inhibit by 50% the bonding of the various antibodies to the parent FP-L peptide immobilized on the dextran matrix (by cysteine). In this series of experiments, the effect of the position of the cysteine in N- or C-terminal and the effect of blocking the C-terminal end or the two N- and C-terminal ends were studied.

It will be noted that the blocked or non-blocked RI analogues are all competitors which are as good as the parent FP-L peptide.

2) Study of the immunogenic properties of the analogues.

The parent (L) peptide and the RIa and RIb analogues were injected into rabbits and the ELISA response with respect to the homologous peptides was measured.

The results are shown with the FL peptide on Table 11 of the specification. The applicants noted that the FL-RIb peptide induced antibody titres 8 times higher in the "Cannes" rabbit.

The recognition of the various analogues by the rabbit anti-peptide antibodies were tested by the same principle as that shown on Table 10 of the specification, using the analogues in solution in the BIAcore system (Table 12, competition test of the specification).

3) Study of the immunogenic properties of the analogues: neutralizing response.

The L and RIb FP peptides were injected into guinea-pigs and the neutralizing response on the virus was measured *in vitro*. The preparations used correspond to peptide analogues bonded to liposomes of the small unilamellar liposome type prepared by the process described by Benkirane et al. (J. Biol. Chem., 268: 26279-26285, 1993). The neutralization test was carried out by the method of Francis and Black (1983) J. Hyg. Camb., 91: 329-334. The results are shown on Table 13 of the specification.

The results are expressed as $\log_{10}$ and correspond to the difference between the titre of the virus incubated with normal serum and that of the virus incubated with serum of the immunized guinea-pig (dilution of the sera 1/20).

The tests were carried out in the laboratory of Professor F. Brown (American Department of Agriculture, Centre for Animal Diseases of Plum Island, Greenport, NY 11944, USA).

It is noted that the effectiveness of the FP-L peptide is similar to that of the same peptide described previously (Rowlands et al., Nature, 306: 694-697, 1983) and that these results are reproduced entirely with the RI FP peptide.

As further detailed in the specification, the *in vitro* neutralization titers of the sera taken at various intervals were followed for 362 days. The animals received a single dose of 100 μg of peptide with aluminium hydroxyde gel as adjuvant. The results showed that the level of the response to the retro-inverso peptide $NH_2$-(C)141-159-OH was similar to that obtained with the L-peptides H-141-159(C)-$NH_2$ and H-(C)141-159-OH up to around 50 days after the inoculation. However, compared with the response to the L-peptides, the response against retro-inverso $NH_2$-(C)141-159-OH peptide

continued to increase beyond 50 days (the neutralizing indices are at least 10-fold higher at 100 days). In the samples collected 262 days after inoculation of the animals, the neutralizing indices of the sera from guinea pigs that received the retro-inverso peptide were still significantly higher than those of the sera from responder animals inoculated with the L-peptides.

4) Protection of swine from foot-and-mouth disease with one dose of the all-D retro peptide corresponding to the immunodominant GH loop encompassing residues 141-159 of capsid protein VP1 of foot-and-mouth disease virus serotype A, sub-type12 (FP peptide).

It has been shown that the retro-inverso FP peptide (serotype A) allows to obtain good results in the pig vaccination. The summary of the obtained results are given below.

Nine pigs were given a single inoculum of 100 μg of the retro-inverso peptide corresponding to the immunodominant GH loop encompassing residues 141-159 of capsid protein VP1 of foot-and-mouth disease virus serotype A, sub-type 12. The peptide was conjugated to activated keyhole limpet haemocyanin and oil-adjuvanted before inoculation. The animals were challenged eleven weeks post-vaccination by exposing them to a pig which had been infected with the virus by inoculation. Two naive animals were included in the challenge study as controls. One of the vaccinated animals was completely unprotected and two developed very small lesions. None of the six remaining animals exhibited any clinical signs but two developed antibodies against non-structural proteins indicating that replication of the virus had occurred. No evidence of replication could be detected in the remaining four animals, either by rise in

neutralizing antibody titre or by production of antibodies against non-structural proteins specific for virus replication.

Further evidence of the use of peptides of the present invention is presented in the attached Nargi et al., Vaccine 17 (1999) 288-2893.

Specifically, the attached describes work relating to the vaccination of swine with an all-D retro peptide corresponding to the immunodominant GH loop encompassing residues 141-159 of capsid protein VP1 of foot-and-mouth diseases virus serotype A, sub-type 12 (FP variant). This article shows that a single inoculation of the all-D retro peptide corresponding to the GH loop of FMDV was able to induce anti-peptide and virus neutralizing antibodies in pigs.

It is important to note that this article relates to the use of a totally retro-inverso peptide of FP peptide from serotype A12 of foot-and-mouth disease virus. The above-described Example 3 of the description relates to the use of a totally retro-partly inverso peptide of FP peptide from serotype A12 of foot-and-mouth disease virus. Thus, the article and the example are submitted to provide sufficient examples of immunoretroid peptides of FP that will retain the requisite immunogenicity and specificity of the parent peptide FP.

Contrary the Examiner's comments, the present specification provides a sufficient teaching of the presently claimed invention.

The Examiner asserts that

> **"the prior art teaches that the skilled artisan cannot reasonably predict how any given chemical modification will effect the immunological properties of any given peptide derivatives (Benkirane *et al.*, 1993; Herve *et al.***

> **1997."** See page 2 of the Office Action dated November 17, 2004 (emphasis in the original).

The Examiner has only provided abstracts of the cited references. In the event the Examiner continues to reject the claims based on the cited references, the Examiner is requested to provide a complete copy of the cited references.

The applicants note that neither reference relates to the FMDV peptides of the presently claimed invention. Moreover, the "drastically altered" characteristic highlighted by the Examiner in the cited Benkirane et al reference relates to an induction of

> "an immune response with an unusually high level of IgG3 antibodies"

Moreover, the cited Benkirane et al reference states that

> "[t]he D-enantiomer produced IgG3 antibodies which react with the homologous peptide as well as with the all L-peptide and the parent protein H3 in solution"

Benkirane et al. apparently was able to make a test the immunoretroids to find reactive species, without an undue amount of experimentation. Again, the Examiner is requested to provide a complete copy of the references to allow the applicants to review the complete teaching of each in the event the Examiner continues to rely of the same to reject the claims.

In ¶3 on page 3 of the Office Action dated November 17, 2004, the Examiner asserts that

> "the disclosure fails to disclose the preparation of immunoretroid peptides"

As noted above, the specification exemplifies immunoretroids of the claimed invention. The specification further exemplifies other immunoretroid peptides of the

invention. The Examiner is requested to further clarification basis for the above-quoted statement in the event the claims continue to be rejected.

As also noted above, one of ordinary skill in the art would be able to, at a minimum, make and screen the immunoretroids of the claims, with a reasonable amount of experimentation, to determine identify species having the required specificity.

Finally, the applicants believe that vaccines may be similarly made, without an undue amount of experimentation, as demonstrated by the above-noted passages from the specification as well as the attached published study.

Withdrawal of the Section 112, first paragraph "enablement", rejection is requested.

The claims are submitted to be in condition for allowance and a Notice to that effect is requested.

It is respectfully requested that the Examiner return an initialed copy of Form PTO-1449, filed with an Information Disclosure Statement on January 31, 2001, to the undersigned. A copy of the same was not received with the Office Action dated November 17, 2004 and the previously-issued Office Actions.

The Examiner is also requested to confirm the acceptance of the drawings filed April 13, 2000, or otherwise provide specific objection or rejection of the same.

Respectfully submitted,

**NIXON & VANDERHYE P.C.**

By: _____

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